Malignant Lymphomas • Research Paper

[haematologica]
2004;89:973-978

Quality of life assessment in elderly patients with aggressive non-Hodgkin's Lymphoma treated with anthracycline-containing regimens. Report of a prospective study by the *Intergruppo Italiano Linfomi*

FRANCESCO MERLI
MARILENA BERTINI
STEFANO LUMINARI
RUGGERO MOZZANA
RAFFAELLA BERTÈ
MASSIMO TROTTINI
CATERINA STELITANO
BARBARA BOTTO
MICHELE PIZZUTI
GIANNI QUINTANA
ALBERTO DE PAOLI
MASSIMO FEDERICO

A B S T R A C T

Background and Objectives. The aim of this study was to evaluate quality of life (QOL) in a group of elderly patients (> 65 years) with aggressive non-Hodgkin's lymphoma (NHL) treated with chemotherapy regimens containing anthracyclines.

Design and Methods. QOL was evaluated in a population of elderly patients with aggressive NHL enrolled in a phase III clinical trial run by the *Intergruppo Italiano Linfomi (IIL)* from 1996 to 1999 to compare two different anthracycline-containing regimens (mini-CEOP vs P-VEBEC). The EORTC-QLQ-C30 questionnaire, which has already been validated in oncology, was used. The questionnaire was administered at the time of diagnosis, half way through the chemotherapy and at the time of restaging.

Results. Ninety-one patients completed pre-therapy and post-therapy questionnaires and they are the subject of this report. Baseline QOL assessment showed a strong correlation of poor values of QOL with anemia and high risk according to the International Prognostic Index (IPI). At the end of treatment no functional scales showed worse values. A significant improvement was observed for pain (p=0.003), appetite (p=0.006), sleep (p=0.015) and global health (p=0.027). Considering only the 50 patients who achieved a complete remission (CR), an improvement was also recorded for emotional state (p=0.10), role (p=0.05), constipation (p=0.04) and global QOL (p=0.05).

Interpretation and Conclusions. The EORTC-QLQ-C30 is feasible even in a population of elderly patients, in whom it had never been tested before. The improvement of QOL at the end of the treatment demonstrated that the symptoms of the disease have a greater negative influence on the patient's life than do the side effects of the therapy.

Key words: quality of life, non-Hodgkin's lymphoma, elderly patients.

Correspondence: Francesco Merli, MD, Servizio di Ematologia, Ospedale S. Maria Nuova, Viale Risorgimento 80, 42100, Reggio Emilia, RE, Italy.
E-mail: merli.francesco@asmn.re.it

From the Unità Operativa di Ematologia, Ospedale S.Maria Nuova, Reggio Emilia, Italy (FM), Unità Operativa di Ematologia, Az. Ospedaliera S. Giovanni Battista, Torino, Italy (MBO, BB), Dipartimento di Oncologia ed Ematologia Università di Modena e Reggio Emilia, Modena, Italy (SL, MF), Medicina Interna, Azienda Ospedaliera S. Antonio Abate, Gallarate, Italy (RM), Divisione di Medicina I, Ospedale Civile, Piacenza, Italy (RB), Medicina Interna, Policlinico Monteluce, Perugia, Italy (MT), Divisione di Ematologia, Ospedale "Bianchi Melacrino Morelli," Reggio Calabria, Italy (CS), Ematologia, Azienda Ospedaliera S.Carlo, Potenza, Italy (MP), Divisione di Ematologia, Presidio Ospedaliero "A.Perrino," Brindisi, Italy (GO), Servizio di Ematologia, Ospedale Civile di Legnano, Legnano Italy (ADP).

It is not only the effectiveness of treatment that must be evaluated in patients, who due to their age do not have very high chances of long-term survival, but also the type of life they are offered during and after chemotherapy. Based on different approaches, elderly patients with non-Hodgkin's lymphoma (NHL) can be treated with the same type of regimens as younger patients, using full dosages of drugs,[1-5] or trying to adapt the traditional chemotherapy treatments to them by reducing the dosage of the drugs[6] or creating treatments designed specifically for the elderly[7-11] with the aim of limiting the risk of treatment-related toxicity and mortality. Several recent studies concluded that the gold standard should be considered full dose CHOP with or without anti-CD20 monoclonal antibody, even for elderly patients.[1-5] In 1996 the *Intergruppo Italiano Linfomi (IIL)* started a prospective trial which compared a CHOP-derived regimen (mini-CEOP) with a MACOP-B-derived therapy (P-VEBEC) for the treatment of elderly patients with aggressive NHL.[12] In addition to the traditional endpoints relating to the effectiveness of the therapies, the study also evaluated the issue of quality of life (QOL) following chemotherapy. QOL has already been evaluated in patients suffering from both aggressive and indolent NHL[13-17] but no study concentrating on a group of elderly patients has ever been published *in extenso.*

Design and Methods

Between June 1996 and December 1999, 264 (232 evaluable for final assessment) patients over 65 years old with diffuse large cell non-Hodgkin's lymphoma were enrolled

in a co-operative phase III trial conducted by the *Intergruppo Italiano Linfomi* and randomly assigned to one of two chemotherapy regimens, mini-CEOP (cyclophosphamide, 750 mg/m^2, day 1; epidoxorubicin 50 mg/m^2, day 1; vinblastine 5 mg/m^2, day 1; prednisone 60 mg/m^2, days 1-5; every 21 days for 4-6 cycles) or P-VEBEC (epidoxorubicin 50 mg/m^2 and cyclophosphamide 300 mg/m^2, and etoposide 100 mg/m^2, days 1, 15, 29, and 43; vinblastine 5 mg/m^2 and bleomycin 5 mg/m^2 day 22, 36, and 50; prednisone 50 mg/m^2, days 1-15). Other criteria for inclusion in the clinical trial were Ann-Arbor stage II bulky-IV, absence of concomitant neoplasms, HIV negativity, good cardiac, renal and respiratory function and no previous treatment for lymphoma. Compulsory treatment with prophylactic antibiotics was not planned and the use of granulocyte colony-stimulating factor (G-CSF) was optional. The staging tests included physical examination, computed tomography (CT) of the chest, abdomen and pelvis, bone marrow biopsy and routine blood chemistry tests. At the end of the chemotherapy patients underwent the same CT scans and any other tests which resulted positive at diagnosis.

Study objectives

The aim of the present study was to evaluate the quality of life of elderly patients with aggressive NHL treated with anthracycline-containing chemotherapy in the setting of a clinical trial.

QOL assessment

QOL was assessed by the *EORTC-QLQ-C30* questionnaire,[18] which has already been used in several studies in patients with NHL and other types of cancer.[19,20] The EORTC QLQ-C30 is a 30-item questionnaire composed of multi-item scales and single items that reflect the multidimensionality of the quality-of-life construct. It incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life scale. The remaining single items assess additional symptoms commonly reported by cancer patients (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea), as well as the perceived financial impact of the disease and treatment. The Italian validated version of the EORTC QLQ-C30 was used in the present study. QOL scales were calculated according to the EORTC scoring manual[21] and raw scores were standardized by linear transformation into ranges from 0 to 100. For the functional scales and the global QOL scales a higher score represents a better level of function. For the symptom scales, a higher score corresponds to a higher level of symptoms.

The EORTC-QLQ-C30 questionnaire was administered at the time of diagnosis before any treatment was given, half way through the chemotherapy (before the day-29 infusion of the P-VEBEC regimen and before the fourth cycle of the mini-CEOP chemotherapy) and at the time of restaging (approximately one month after the end of the chemotherapy). The questionnaire was administered by a nurse whose task was to verify the patient's compliance. The nurse was instructed to ask the questions with no further comment. Any clarifications requested on the questions had to be as brief as possible.

Patients were considered eligible for the evaluation of quality of life if they had been given at least the baseline and final questionnaire.

Statistical methods

Proportions were compared by Fisher's exact test. Comparison of quality of life scores between groups and at different phases of treatment were performed using analysis of variance tests for paired samples. A probability of $< 5\%$ was considered statistically significant for all evaluations. The software *Statistical Package for Social Sciences (SPSS)* for Windows, release 10.0, was used for all the statistical analyses.

Results

Recruitment

Seventeen out of 40 centers participating in the clinical phase III trial agreed to participate in the QOL study; these centers provided 76% of all cases included in the clinical trial. Pre-therapy questionnaires were received from 156 patients. Among the 156 patients who completed the baseline questionnaire 65 patients did not complete the final one: 30 due to interruption of the therapy because of toxicity or disease progression, the remaining 35 due to incompleteness of one of the two questionnaires or missing questionnaires.

The group of 91 patients who also completed the post-therapy questionnaire are the subject of the present report. Sixty-four patients had also completed the intermediate questionnaire and were available for an intermediate evaluation. The clinical characteristics of the 91 patients are shown in Table 1.

Patients were equally distributed in terms of treatment centers so that the prophylactic measures taken to reduce toxicity of chemotherapy (anti-emetics, antibiotics) could not have induced a difference between the two groups (*data not shown*).

Baseline QOL assessment

Baseline QOL assessement and clinical data were available for all 91 patients. The values of single QOL scales are reported in detail in Table 2 and are correlated with the presence of clinical features with known

Table 1. Characteristics of the 91 patients in whom QOL was evaluated.

	All pts. (n=91)	
Age (years)		
Median (Range)	73	(66-85)
	N	%
Gender		
Male	31	34
Female	60	66
Stage		
I	3	3.3
II	19	20.9
III	23	23.3
IV	46	50.5
Performance Status		
0-1	73	80.2
2-3	18	19.8
Hemoglobin (g/dL)		
≥ 12	49	53.8
< 12	42	46.2
Lactate dehydrogenase		
≤ normal value	42	46.2
> normal value	49	53.8
Age-adjusted IPI		
0-1	47	51.6
2-3	44	48.4
Response		
CR	50	54.9
Less than CR	41	45.1

adverse prognostic value. Among the evaluated clinical parameters, anemia and IPI were strongly associated with poorer values of QOL scales (9 and 10 out of 16, respectively) while poor performance status showed an intermediate strength association with poor QOL results.

Change in QOL during treatment

Analysis of the final QOL assessment showed all multi and single item scales had improved except diarrhea and social activity which had deteriorated slightly. Among the other scales a statistically significant improvement was observed for pain (p=0.003), appetite (p=0.006), sleep (p=0.015) and global health (p=0.027). The results are summarized in Table 3.

An intermediate QOL assessment was also available for 64 patients. An early improvement was observed for the pain score (p<0.0001) while a worsening of nausea and vomiting score (p=0.007) was recorded after the administration of the first half of treatment. A delayed improvement was observed for fatigue (p=0,026) and global health scales (p=0.015; see Figure 1).

QOL and response to the therapy

Among the 91 patients who completed the QOL questionnaire both before and after therapy, 50 patients (55%) obtained a complete response (CR), 34 patients (36%) had a partial response (PR) and 7 patients (9%) had no response or progressive disease. Comparing QOL results between patients in CR with those in PR or less, the improvement of the variables which changed positively in the overall population (pain, appetite, sleep, overall health) was confirmed only in the first group. Moreover, patients in CR achieved a benefit in terms of emotional (p=0.01), role (p=0.05), constipation (p=0,04) and global QOL (p=0.05) scores (Table 4). On the contrary, in patients with less than CR, no parameter improved significantly at the end of therapy (*data not shown*).

No significant differences were found between patients treated with P-VEBEC and those treated with mini-CEOP (*data not shown*).

Discussion

Since the beginning of the 1980s, the idea that cure of NHL was a reasonable objective even in patients over 65 years old has made much headway. In fact, although the overall percentages of CR and failure-free survival (FFS) are lower than those in younger patients, surveys demonstrate that the percentages of CR in elderly patients fluctuate between 46 and 77%,[3,11] with a strong possibility of this group maintaining long-lasting remissions. However, these patients have a limited life expectancy and the price paid by elderly patients in terms of quality of life to obtain the cure of the disease has never been verified.

In the present study we evaluated the issue of QOL in a group of elderly patients with aggressive NHL registered in a phase III clinical trial by the *Intergruppo Italiano Linfomi* comparing the feasibility of and responses to two different regimens specifically devised for the elderly (mini-CEOP vs P-VEBEC) with different timings and dose intensities.[12]

A questionnaire which had already been tried and tested on cancer patients seemed to be the most suitable tool. No evaluation of this type on a population of elderly patients has ever been published. One reason for this is probably the low reliability of the answers given. The idea of this questionnaire being proposed to the

Table 2. Quality of life and clinical parameters at diagnosis.

	N	Phisycs Function	p	Role Function	p	Cognitive Function	p	Emotional Function	p	Social Activity	p	Fatigue	p
Hemoglobin (g/dL)													
≥ 12	49	71.0 (41.5-100)	0.010	74.8 (43.2-100)	0.010	90.1 (77.9-100)	0.004	75.5 (56-95)	0.08	84.8 (66.8-100)	0.005	25.5 (4.6-46.4)	0.0001
< 12	42	53.3 (18.0-88.5)		55.5 (17.5-93.5)		79.3 (57.6-100)		66.6 (38-95.3)		69.8 (39.3-100)		44.5 (17.3-71.8)	
ECOG Performance Status													
0-1	73	67.3 (34.6-100)	0.008	71.2 (36.8-100)	0.004	86.7 (69.4-100)		71.4 (46.4-96.4)		80.5 (55.8-100)	0.05	32.5 (5.9-59.1)	
2-4	18	44.4 (14.8-73.9)		44.4 (10.1-78.7)		78.7 (59-98.3)		71.2 (48.7-93.8)		67.2 (40.2-94.3)		41.7 (20.5-62.9)	
Age-Adjusted IPI													
0-1	47	71.9 (44.2-100)	0.007	78.2 (47.4-100)	0.001	89.1 (75.4-100)	0.05	76.4 (53.8-99)	0.030	86.4 (68-100)	0.001	25.7 (1.5-49.9)	0.001
2-4	44	53.1 (19.7-86.5)		53.0 (16.1-89.9)		81.4 (60.4-100)		65.5 (40.3-90.7)		68.9 (39.8-98.0)		43.4 (19-67.8)	

	N	Pain	p	Dyspnea	p	Sleep disturbance	p	Appetite loss	p	Global Health	p	Global QOL	p
Hemoglobin (g/dL)													
≥ 12	49	19.1 (0-43.9)		9.5 (0-29.9)	0.040	15.7 (0-43.6)		18.4 (0-46.5)	0.03	63.2 (45.9-80.6)	0.009	62.5 (42.5-82.5)	0.01
< 12	42	29.4 (0-61)		20.6 (0-50)		30.2 (0-62.1)		33.3 (0-67.8)		50.7 (24.0-77.6)		49.6 (21.9-77.2)	
ECOG Performance Status													
0-1	73	18.5 (0-45.5)	0.0001	13.2 (0-37.3)		21.5 (0-50.6)	0.05	20.6 (0-50)	0.004	59.5 (35.7-83.5)	0.08	57.5 (32.6-82.3)	
2-4	18	45.4 (21.3-69.5)		20.4 (0-51)		37 (12.4-61.6)		44.4 (4.8-84)		49.0 (32.4-65.7)		52.7-2976.5	
Age-Adjusted IPI													
0-1	47	16.3 (0-40.9)	0.009	9.2 (0-27.2)	0.03	15.6 (0-40.5)	0.003	19.2 (0-49.3)	0.05	63.4 (43.6-83.2)	0.02	62.6 (41.5-83.8)	0.02
2-4	44	31.8 (1.6-62)		20.5 (0-51.2)		34.1 (1.5-66.7)		31.8 (0-64.7)		51.5 (26.6-76.4)		50.3 (23.6-77.1)	

The table shows correlations between single baseline QOL scales and the presence of baseline clinical characteristics generally associated with poor outcome. For each scale the median result is reported with 95% Confidence Interval. p values were assessed by means of between groups non-parametric comparisons tests and are reported when statistically significant (< 0.05). Constipation, diarrhea, nausea and vomiting and financial scales are not reported because no correlation with any clinical feature was found.

patients by a nurse (despite the fact that EORTC-QLQ-C30 was designed for self-compilation) was intended both to evaluate the patient's compliance to the questions and to avoid interference from the patient's relatives who could condition the replies or even answer on the patient's behalf. When interpreting our results, it should be noted that some symptoms examined by the EORTC-QLQ30, such as sleeping disturbances, loss of appetite or the feeling of pain might be influenced by a depressive state that is not rare in a population of elderly patients; this represents a limitation of the EORTC-QLQ30 that could be overcome only with the use of a specific psychologic questionnaire on anxiety and depression such as the Hospital Anxiety and Depression (HAD) scale.

The results of the present study demonstrate that the EORTC-QLQ-C30 questionnaire is also valid when used on a population of elderly patients. Based on our results the reliability of the answers was good and supported by the correspondence of the evaluation of the state of health of the patients from the answers to questionnaires administered at diagnosis and the IPI. A second aspect is the coherent and complete overlap of initial and final answers to the question on financial status. This result was expected, as the people who were studied were retired and no longer carried out any profes-

Table 3. Results of QOL at diagnosis and at the end of treatment (91 patients).

QoL Scales	*Start of treatment (95% CI)*	*End of treatment (95% CI)*	*P*
Functional scales			
Physical function	62.8 (29.5-96.1)	62.6 (33.0-92.1)	ns
Role function	65.9 (30.1-100)	71.4 (40.1-100)	ns
Cognitive function	85.1 (67.1-100)	86.4 (68.8-100)	ns
Emotional function	71.4 (47.0-95.8)	75.7 (51.4-100)	ns
Social activity	77.8 (52.3-100)	75.3 (47.1-100)	ns
Symptom scales			
Fatigue	34 (8.3-59.7)	30 (7.1-52.9)	ns
Pain	23.8 (0-52.3)	14.6 (0-37.1)	0.003
Nausea and vomiting	6.4 (0-19.3)	6.2 (0-18.5)	ns
Dyspnea	14.6 (0-40)	13.6 (0-34.7)	ns
Sleep disturbance	24.5 (0-54.7)	16.1 (0-40.1)	0.015
Appetite loss	25.3 (0-57.3)	14.7 (0-38.6)	0.006
Constipation	20.5 (0-48.1)	17.6 (0-42.6)	ns
Diarrhea	2.9 (0-14.7)	5.1 (0-23)	ns
Financial impact	96.7 (83.5-100)	96.7 (83.5-100)	ns
Single item scales			
Global Health	57.5 (34.5-80.4)	63.7 (41.5-85.9)	0.027
Global QoL	56.5 (32.0-81.1)	61.5 (39.7-83.2)	ns

Table 4. QOL scales showing a significant improvement from baseline levels for patients achieving CR (50 patients).

QoL Scales	*Start of treatment*	*End of treatment*	*p*
Functional scales			
Role function	64.7 (26.4-100)	76.7 (44.9-100)	0.05
Emotional function	70.7 (43.7-97.7)	79.7 (58.3-100)	0.01
Symptom scales			
Pain	21 (0-49.5)	11.3 (0-30.2)	0.02
Sleep disturbance	23.3 (0-54.3)	11.3 (0-29.9)	0.007
Appetite loss	28 (0-61.2)	9 (0-27.2)	0.0001
Constipation	25.3 (0-55.1)	17.3 (0-46.1)	0.04
Single items scales			
Global Health	57.3 (34.7-79.9)	68 (49.3-86.7)	0.011
Quality of Life	56.7 (32.4-81)	65.3 (45.7-84.9)	0.05

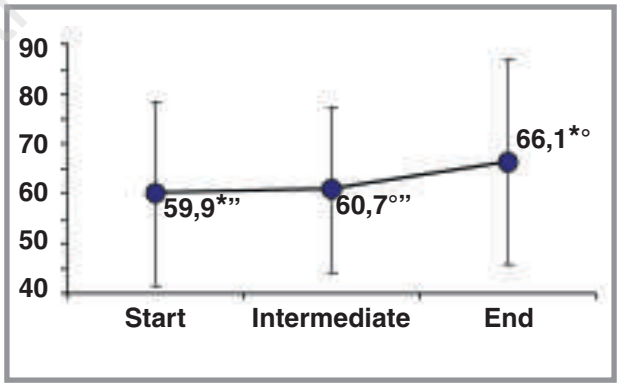

Figure 1. Modification of Global Health scale during treatment (64 evaluable patients) showing the mean value at the start of the treatment, at the intermediate evaluation and at the end of therapy; *p=0.039; "p= 0.75 (NS); °p= 0.015.

sional activity. As far as the analysis of the results is concerned, the most significant data are that no functional scale showed worse values at the end of the therapy than at diagnosis. This demonstrates that the symptoms of the illness have a greater negative influence on the patient's life than do the side effects of the therapy. This is also confirmed by the data relating to the 64 patients who had completed the intermediate questionnaire from which it was seen that the QOL is not further reduced during therapy.

The most significant data are related to the two overall questions on health and quality of life; the first improved for the overall sample of patients, while the second improved significantly only in those patients obtaining a CR. Comparing the group of patients in CR, in whom scores for 8 out of 16 functional scales improved, with patients who did not obtain CR, in whom no score improved, we can conclude that the there is no cost in terms of QOL for the cure of the disease.

Our study did not demonstrate a statistically significant advantage in terms of response rate in patients

with good initial quality of life compared with those with poorer QOL. The hypothesis that the quality of life estimated with EORTC-QLQ-C30 may have a prognostic role, as described for multiple myeloma,[22] is still an open question.

Finally a reply cannot be given to which of the two administered chemotherapy regimens had the better impact on QOL. This is partly due the small size of the sample when divided into groups and partly due to a suggested bias between the data of the P-VEBEC and mini-CEOP groups which showed a higher prevalence of patients in CR in the second group. In conclusion our study demonstrated that QOL assessment is feasible in elderly patients with NHL and confirmed that future studies on elderly patients suffering from NHL should aim to eradicate the disease rather than palliate the symptoms. We feel that evaluating a larger number of patients would be very useful in helping to confirm the results of our study.

FM designed the study and wrote the manuscript. MB and RM collaborated in designing the study. SL was responsible for the statistical analyses and collaborated in the manuscript preparation. RB, MT, CS, BB, MP, GQ and ADP were responsible for the care of patients and data collection. MF revised the article critically. All authors gave their final approval of the version to be published. We thank Mrs. Luciana Costantini for her assistance in the process of data collection.

The authors reported no potential conflicts of interest.

Manuscript received June 13, 2003. Accepted May 30, 2004.

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